January 8, 1951.

Dear Kim and Lil-

Thanks very much for letting me see your Ms- it certainly sets forth a most interesting concept. I hope you will be able to find the immediate basis of the adaptive leaps before too long. By coincidence, I've been somewhat immersed in colicins myself lately, having run into them repeatedly in tests for inter-strain crossing, and wishing to use resistance patterns as genetic markers. Fredericq has been extremely cooperative, and went to some trouble to send his major colicin producing types, which we are working up now. He finds that both B and K-12 are susceptible to almost all of the colicins he has found, so that they are useful indicator strains.

Since you have evidently sent in the ms. (under some pressure!) I take it that you are not interested in a discussion of the paper as such, but my critical cortex impels me to slip in a comment or two. I could find nothing lacking in the content, but the presentation does show signs of haste, and it is therefore somewhat difficult to read, in places; redundant in others. It might help the casual reader if the cycles were referred to as a sort of repeated reisolation or renewal of the cultures from one or a few cells, rather than as a "suppression of all mutants". On page 11, I think the case is somewhat overstated, particularly with respect to a) selective factors specifically favoring h' during part of the history of a culture, and b) the time which would be required to approach the equilibrium you mention in the complete absence of selective differentials. Finally, it is not quite fair to generalize from Lieb's value, since she found a variety of mutation rates for different h- mutants, which straddled the mutation rates to h-. This kind of calculation has the same sort of merit as the ones by N. & Sz. to which you objected (which is not to say that it is without value!)

This is perhaps very much uncalled for, so I don't expect you to pay any attention to it, but I am left with the impression that this is a good paper which might be a superb one. You may not want to bother to recall the ms. simply to acknowledge N & Sz. current paper, but there should be a mention of Mr Stocker's work on S. typhimurium (J. Hyg., Dec. 1949). He found and interpreted similar cycles, but was able to demonstrate a mutational equilibrium at the predicted value (from the rates). Your generalizations would have much more force if the analysis reviewed these other examples. If the tables were turned, it would take a cataclysm to make me recall a paper once sent in, but that might just be a weakness in my character.

So far, I haven't carefully read the N&Sz paper, but have talked to Aaron about it. Aaron is aware of the inconsistency with the nonaccumulation of mutants in resting cultures, and has verified it (taking account of phenotypic lag) in cultures blocked by tryptophane exhaustion. He tried to set up his chemostat (atrocious name!) to run very slowly, to find the changeover point, but the machine loses its self-regulation at very low rates. He may think that "lag" is a special physiological condition in which mutations

do not occur. This of course does not agree very well with the time-dependence during growth: he is as puzzled about it as anyone. Right now they are studying effects of changing medium conditions, as well as adding weak mutagens (e.g. methyl-purines) to the medium.

Lately, I've been working mainly on cleaning up loose ends innthe heterozygote work, and in interstrain crosses. The prototroph-S^r selection method has worked out very well now, about 10% of coli isolates from human urine cultures crossing quite freely with K-12 (originally isolated from the same source). We are akso starting some immunizations.

Bussard has been very great fun; it's too bad he doesn't have his wife here too, for he tends to be rather homesick, and only recently resolved definitely to stay here for next semester. We have been doing some little work together, especially on paper electrophoresis of lactase.

Your latest datum on UV effect is most interesting. Is it possiblenthat the damage is not primarily nuclear, but that if a small cell should "bud" off, with a limited amount of damaged "cytoplasm", it will be able to recover more rapidly? In E. coli, the picture is strikingly similar to yours now, except that I don't have much evidence for balanced lethals, but this may be due to intracellular selection or whatnot. There are genetic effects (homozygotization; haploidization) which I think are induced, at least indirectly, by UV in diploid cells, but which could have no counterpart on haploid heterokaryons. Since we may both be writing up our material concurrently, may we agree to exhange mss. at an early stage? Probably, and preferably, your work will be published first, because I have a number of tag ends on diploid behavior to worry about, especially the "Lwoff effect", i.e., the UV-activation of lysogenic phage, which results in the lysis of phage-carrying cells. Thus, lysogenic bacteria, at certain doses, are killed rather more rapidly than sensitive,uninfected. This certainly messes up any kinetic analysis of U^V killing, which, as you know, I have no confidence in anyhow.

I'm sorry to hear that the Army wants you, mainly out of pity for our poor servicemen. If worst comes to worst, would you consider working in BW. Besides Werner Braun's outfit, there is also a group run by U. Cal. at Berkeley and Oakland, but the intellectual milieu is equally dim, which is possibly the fault of BW rather than the men. "Captain" Krueger is in charge of the Cal. organization, and also chairman of the university's Bact. Dept.

I wish I knew more about FJ's expedition: I hope it's not down the garden path. A couple of years ago, Esther and I were mildly excited by the elicitation of Lac- in K-12 by butyl galactoside, but this is almost certainly selection. I have the feeling that this is mentioned somewhere, besides Esther's thesis, but I can't find it.

Have a happy new year yourselves, if you can,

Sincerely,

Joshua Lederberg

January 10, 1951.

POSTSCRIPT.

Kim- I just retrieved the letter and ms. to add the following.

After a few hours thought, I am convinced that the argument on p. 11 is incomplete. If there is no specific selection against X-, and the mutation rate to X- exceeds that to X+, then periodic selection cannot possibly influence the probability that a single X gene sampled from a large universe, will be + or -. The key is the term periodic selection, which is in fact a periodic sampling, at random, of the elements of an existing population for the redevelopment of a new one. The periodic selection (all other things being equal) is precisely equivalent for example to stochastic survival of a non-specific killing agent (like heat, spore transport, or an inoculating pipette), as far asi its effects on the mean proportions of X+ and - are concerned. What period selectipn will do, of course, is to broaden the disperäion of the distribution of the mutants, so that instead of having a hundred cultures each with 1% mutants (say of all auxotroph possibilities), you may end up with 100 cultures, one completely auxotrophic. But for the equilibrium situation which you set up on p. 11 this can make no difference.

A point worth emphasizing is that periodic selection can occur only in asexual populations, since it is required that the adaptive mutation be isolated from the existing auxotrophs (or equivalent). However, in some ways, this is reminescent of Sewall Wright's "drift" hypothesis, except that the fixation results from the inherent dynamics rather than imposed isolations.

If I may make a suggestion, it may be worthwhile to depict in a graph what the theoretical evolutionary history of a culture is likely to be under the postulates of your system. I would picture it is something like: